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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ARIANI, KADE	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
12/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,291	YONEHARA ET AL.	
	Examiner	Art Unit	
	KADE ARIANI	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11 and 13-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-11 and 13-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on July 19, 2010, has been received.

Claims 1, 2, 4-11, and 13-31 are pending in this application and were examined on their merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/19/2010 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The added material which is not supported by the original disclosure is as follows:

In claim 1 (lines 15-16) "the tetrazolium compound and the sodium azide being present at the same time during the redox reaction". Because the specification while provides support for "adding a tetrazolium compound and sodium azide to hemolyzed sample, in general. It does not provide support for the tetrazolium compound and the sodium azide being present at the same time during the redox reaction".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, and 4-11, and 13-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Komori et al. (European patent application, EP1 002874 A2,

Published June 24th, 2000) in view of Yoshida et al. (Eur. J. Biochem., 1996, Vol. 242, 499-505) and Ishimaru et al. (Patent number 6,127,138, Date of Patent Oct. 3, 2000), and further in view of Montellano et al. (Biochemistry, 1988, Vol. 27, pp. 5470-5476), Kwan et al. (US patent No. 5,556,788), Fry et al. (J. Nutr., 1982, Vol. 112, p.1631-p.1737) and of Ledis et al. (US patent No. 5,731,206).

Claims 1, 2, and 4-11, and 13-31 are drawn to a method of measuring an amount of a glycated protein as an analyte in a sample, comprising: causing a fructosyl amino acid oxidase (FAOD) for degradation (degradation FAOD) to the sample as a pretreatment so that a free amino acid that is glycated present in the sample as a contaminant is degraded and removed form the sample by the degradation FAOD, the pretreatment further comprises removing hydrogen peroxide generated from a redox reaction between the degradation FAOD and the free amino acid that is glycated, adding a protease to the sample to give a degradation product of the analyte remaining in the sample, adding a fructosyl amino acid oxidase for measurement (measurement FAOD) to the sample treated with the protease to cause a redox reaction between the measurement FAPD and the degradation product of the analyte, and measuring an amount of hydrogen peroxide generated by the redox reaction to determine the amount of the analyte, wherein the redox reaction is conducted in the presence of a tetrazolium compound and sodium azide, the tetrazolium compound and sodium azide being present at the same time during the redox reaction, wherein the measurement FAOD is added after the adding of the protease to the sample, wherein the measurement of the amount of hydrogen peroxide comprises adding a color-developing substrate to allow a

redox reaction between the color-developing substrate and the hydrogen peroxide, and measuring an amount of color developed by the color-developing substrate to determine the amount of hydrogen peroxide further comprises, adding N-(carboxymethylaminocarbonyl)-4,4'-bis(dimethylamino) diphenylamine sodium salt as a color-developing substrate to a reaction solution of the redox reaction in the presence of a surfactant, a concentration of the tetrazolium compound in the reaction solution is in a range from 0.5 to 8 mmol/1, a concentration of the sodium azide in the reaction solution is in a range from 0.08 to 0.8 mmol/1, a concentration of the surfactant in the reaction solution is in a range from 0.3 to 10 mmol/1, and a pH of the reaction solution is in a range from 7.0 to 8.5, the tetrazolium compound is 2-(4-iodophenyl)-3-(2,4-dinitrophenyl)-5- (2,4-disulfophenyl)-2H-tetrazolium salt, and a measuring kit for measuring a glycated protein.

Komori et al. teach a method of measuring an amount of a glycated protein as an analyte in a sample, comprising: causing a fructosyl amino acid oxidase (FAOD) to act on a glycated amino acid present in the sample so that the analyte remains in the sample and the glycated amino acid is removed form the sample by degradation; degrading the analyte with a protease to give a degradation product of the analyte either before or after causing the fructosyl amino acid oxidase to act on the glycated amino acid; then causing a fructosyl amino acid oxidase to act on a proteolytic degradation product of the analyte to cause a redox reaction in the presence of a tetrazolium compound and sodium azide; and measuring an amount of hydrogen peroxide generated by the redox reaction to determine the amount of the analyte, wherein the

measurement of the amount of hydrogen peroxide comprises adding a color-developing substrate to allow a redox reaction between the color-developing substrate and the hydrogen peroxide (page 2, 0002-0004, and page 4 0029 and 0030). Komori et al. teach adding a tetrazolium compound prior to the redox reaction or pretreating a sample with a tetrazolium compound to eliminate the influence of any reducing substance (Page 2 0010, and page 8 0072), and further teach the formation of hydrogen peroxide due to the oxidation of glycated proteins by the action of FAOD enzyme, and further teach both glycated peptides (proteins) and glycated amino acids can be subjected to the action of FAOD and glycated proteins and peptides are treated with a protease before its treatment with FAOD (Page 4, Lines 7-9). Komori et al. teach the color developing substrate N- (carboxymethylaminocarbonyl)-4,4'-bis(dimethylamino) diphenylamine sodium salt (DA-64) as (Page 4, Lines 3-5) and teach adding a surfactant so that its concentration in the treating solution falls in the range of 0.01- 5% by weight (Page.6 Line 5) and the concentration of tetrazolium compound (WST-3) is 1 mmol/L (Page 8, Lines 26 and 27). Komori et al. teach a peroxidase (POD) having a concentration equal to 219 KU/L (Page 17, 0095) and a reducing agent are added to the sample (Page 2, Line 12). Also according to Sigma-Aldrich catalogue active form of a metalloproteinase in 10mM MES buffer, containing 0.25 mM sodium chloride and 5 mM calcium chloride and 0.01% sodium azide. Komori et al teach non-ionic surfactants such as Triton X-100 series, Tween series, Brij series and the like (page 5-6, 0044). The pretreatment is usually carried in a buffer and further recites CHES, CAPSO, CAPS, phosphate, Tris, EPPS, HEPES, pH range 8-12 (Page 6, 0047). Komori et al. teach FAOD treatment is

carried out in the same buffer used for protease treatment, using Tris-HCl, EPPS, or PIPES buffer, the concentration of FAOD in the reaction solution is 50-50,000 U/L and pH of 6-9 (Page 6, 0052,0055) and 0.146 mM DA-64 (Page 17, 0095). Komori et al. also teach uricase (page7, 0066) and bilirubin oxidase (Page 7, 0064). Komori et al. teach also teach hydrogen peroxide formed by oxidation of glycated amino acids with FAOD (page 3 0030). Komori et al. teach FAOD treatment can be done separately or simultaneously, protease treatment + FAOD treatment (step 3), FAOD treatment + redox treatment (step 4), and the order of adding the FAOD is not limited (p.7 0061 step 3 and 0062). Therefore, Komori et al. teach pretreatment with a measurement) FAOD, and adding a measurement FAOD during the redox reaction. Komori et al. further teach conditions of the FAOD treatment are determined as appropriate depending on the type of FAOD used, the type and the concentration of the glycated proteins (p.6 0054).

Komori et al. do not teach a fructosyl amino acid oxidase for degradation (degradation FAOD), a fructosyl amino acid oxidase for measurement (measurement FAOD), tetrazolium compound and sodium azide are present at the same time during the redox reaction, aging a solution containing tetrazolium compound and sodium azide, a free amino acid that is glycated, removing the hydrogen peroxide using a catalase, and a measuring kit. However, Yoshida et al. teach a fructosyl amino acid oxidase (FAOD) which is active towards a glycated amino acid (fructosyl-Z-lysine), and that the enzyme did not use glycated proteins directly as its substrate, but it only used glycated protein (glycated human serum albumin or HAS) as substrate after it was treated with a protease (Abstract lines 1-4 and “Materials and Methods”, Substrates, line 1). Yoshida

et al. further teach FAODs with different substrate specificities, applicable in the enzymatic measurement of glycated proteins, for measurement of glycated albumin and glycated HbA (Introduction 2nd column 1st paragraph and p.503 Table 4., see 1st and 3rd columns). The FAOD(s) taught by Yoshida et al. are equivalent of the FAOD(s) enzymes disclosed in the specification and perform the same function specified in the claims. Therefore, the claimed "degradation FAOD" is met by Yoshida et al., Yoshida et al. further teach the amount of total glycated serum protein is known to be a more sensitive indicator of the great fluctuations in the blood glucose level generally associated with insulin-dependent diabetes. The FAOD from *P. janthinellum*, which showed higher activity toward Fru-Val, is expected to be applicable to the enzymatic determination of glycated HbA (whose N-terminal valine residue is glycated) (p.504 2nd column 3rd paragraph).

Fry et al. teach the formation of free amino acids that are glycated in parenteral nutritional solutions used for intravenous feeding (reaction products between glucose and free amino acids in glucose and amino acid solutions) (p.1631 Introduction 1st column 1st paragraph lines 1-6, and p.1636 1st column 2nd paragraph). Fry et al. further teach these products can enter circulation of the patients infused with these solutions during intravenous feeding (p.1636 2nd column 3rd paragraph).

Further motivation is in Ishimaru et al. who teach measuring an amount of a glycated protein in a sample by causing an oxidoreductase (an enzyme that catalyzes an oxidation-reduction or redox reaction) to act on glycated protein and measuring the amount of the product based on the action of the enzyme (Col.1, lines 61-66). Ishimaru

et al. teach measuring a glycated protein for the purpose of the diagnosis of diabetes and further teach the method is applicable to a general-purpose examining apparatus with lower cost for a shorter period of time (Col. 2, Lines 41-44). Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the invention was made, knowing the presence of a contaminant glycated amino acid in the sample (that can interfere with the measurement) and the substrate specificities of the FAOD enzymes, would have been motivated to try and to modify the method as taught by Komori et al. by using FAOD enzyme(s) as taught by Yoshida et al. to degrade/remove a contaminant glycated amino acid present in a sample in order to provide a method for measuring an amount of glycated protein in a sample with a reasonable expectation of success, because Komori et al. teach glycated amino acids can be subjected to the action of FAOD, and because Yoshida et al. teach degradation FAOD that are applicable in the enzymatic measurement of glycated proteins. The motivation as taught by Yoshida et la. would be to provide a more sensitive enzymatic method.

Kwan et al. teach storing a reagent comprising tetrazolium compound by leaving the solution to stand at temperature in the range of 20-60ºC for 6 to 120 hours (column 4 lines 46-48), adding sodium azide to a control reagent and incubating for 4 days at 37ºC (column 6 lines 37-50). Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to age a solution containing tetrazolium compound and sodium azide according to the teachings of Kwan et al.

Ishimaru et al. teach hydrogen peroxide generated by the FAOD (FAOD reaction product) can be removed by using catalase (column 9 lines 27-39). Also, Montellano et

al. teach azide anion inhibit catalase and horseradish peroxidase, and using 0.15-0.6 mM sodium azide to inhibit catalase (p.5470 Introduction, p. 5471, 3rd Paragraph). Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to add sodium azide to the tetrazolium compound in the method as taught by Komori et al. to inhibit catalase and to stop the redox reaction of catalase.

Further motivation for the tetrazolium compound and sodium azide to be present at the same time during the redox reaction, is in Ledis et al. who teach using sodium azide and sodium salts in conjunction with electron withdrawing compounds having sulfonic acid and nitro groups (column 5 lines 65-66 and column 6 lines 55-56, and column 10 lines 41-46) in a reagent system for selective hemolysis. It must be noted that tetrazolium compound is electron withdrawing compound with a sulfonic and a nitro groups.

Therefore, a person of ordinary skill in the art at the time the invention was made, would have been motivated to modify the method as taught by Komori et al. and to remove the hydrogen peroxide generated from a redox reaction between the degradation FAOD and the glycated free amino acid, and to add sodium azide to the tetrazolium compound in the reagent according to the teachings of Ishimaru et al. and Montellano et al. and Ledis et al. to provide an improved method for measuring an amount of glycated protein in a sample with a reasonable expectation of success, because Ishimaru et al. teach removing the hydrogen peroxide generated by the FAOD by using catalase, and because Montellano et al. teach azide anion inhibit catalase, and using 0.15-0.6 mM sodium azide. The motivation would be the ability of sodium azide to

inhibit catalase and to prevent bacterial contamination, and also because Ledis et al. teach using sodium azide in conjunction with electron withdrawing compounds having sulfonic acid and nitro groups.

Accordingly, once the method of measuring an amount of a glycated protein in an analyte was established, providing a measuring kit to determine the amount of the glycated protein would become obvious. The motivation as taught by Ishimaru et al. would be to provide a kit for the purpose of the diagnosis of diabetes.

Answer to Arguments

Applicant's arguments filed on 07/19/2010 have been considered but they are not persuasive.

Applicant argues that Applicant have found for the first time that the free amino acids that are glycated actually affect the measurement system of glycated protein, and a solution to address such problems.

This argument is considered but is not found persuasive because, as mentioned immediately above, Komori et al. teach both glycated amino acids and glycated proteins can be subjected to the action of FAOD.

Moreover, Fry et al. teach the formation of free amino acids that are glycated in parenteral nutritional solutions used for intravenous feeding (reaction products between glucose and free amino acids in glucose and amino acid solutions). Fry et al. further

teach these products can enter circulation of the patients infused with these solutions during intravenous feeding. Therefore, a person of ordinary skill in the art at the time the invention was made would have recognized the presence of free amino acids in the blood sample of patients infused with these solutions, also a person of ordinary skill in the art at the time the invention was made would have recognized that any glycated amino acids (unrelated to the glycated protein to be measured) in the blood sample would interfere with the measurement of the glycated protein.

Applicant argues that Komori do not teach whether the FAOD can be added before the protease treatment so as to allow the FAOD to act on a glycated amino acid present in the sample and thereby degrade the glycated amino acid present in the sample, and Komori does not provide any guidance or any experimental data showing that the FAODs, would be functional if they were added prior to the addition of the protease, and none of the cited references remedy the deficiencies of Komori. These arguments are considered but are not found persuasive because, as mentioned immediately above, Yoshida et al. teach a fructosyl amino acid oxidase (FAOD) which acts on a glycated amino acid (fructosyl-Z-lysine) and did not use glycated proteins and can only act on glycated proteins after protease treatment and which is applicable in enzymatic determination of glycated hemoglobin. Therefore, at the time the invention was made a person of ordinary skill in the art would have recognized that the FAOD of prior art would be functional if they were added prior to the addition of the protease. Thus, a person of ordinary skill in the art at the time the invention was made would have been motivated to use said FAOD in a method of measuring an amount of glycated

protein with a reasonable expectation of success. Because, Yoshida et al. teach the enzyme is applicable in enzymatic determination of a glycated protein.

Applicant argues that none of the references teach or suggest for "the tetrazolium compound and the sodium azide being present at the same time during the redox reaction". This argument has been considered but is moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on IFP.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-830.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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/Kade Ariani/
Examiner, Art Unit 1651